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(54) Title: A COMPOSITION FOR ADMINISTRATION BY THE INTRANASAL, SUBLINGUAL OR VAGINAL ROUTE

(57) Abstract

A composition for therapeutic or diagnostic use, suitable for administration by the intranasal, vaginal and sublingual route, comprising a protein–antibody complex and at least one pharmaceutically acceptable ingredient.

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A COMPOSITION FOR ADMINISTRATION BY THE INTRANASAL, SUBLINGUAL OR VAGINAL ROUTE

* * * * * * * *

The present invention relates to a composition for therapeutic or diagnostic use, suitable for administration by the intranasal, sublingual or vaginal route and which comprises a protein-antibody complex.

More particularly, the present invention refers to a composition of protein, peptides and polypeptides for administration by the intranasal, sublingual or vaginal route.

It is known that many pathologies can be treated with proteins, peptides or polypeptides [hereinafter referred to collectively as protein(s)].

Due to DNA recombination technology, an increasingly greater number of highly purified proteins are available which can be used in the treatment of various human pathologies.

Because of the degradation they undergo during passage through the gastrointestinal tract, administration of proteins by the oral route is not very effective. Administration by the injectable route is therefore the most frequently used method of administration, although the method has many disadvantages, for example:

a) poor tolerance by patients, especially in treatment of chronic diseases;
b) a consequent risk of poor compliance with the dosage when the protein is not a "life saver";
c) difficulty of carrying out self-administration by the patient;
d) possible non-availability of suitable surroundings for carrying out the procedure in an aseptic manner;
e) variability of absorption of protein administered by the subcutaneous route (considerable variability has been documented both for insulin and growth hormone), and

f) administration by injection does not simulate the physiological secretion rhythm of the endogenous protein which has to be administered.

A considerable need is therefore felt to find alternatives routes for administration of proteins.

It is also known that administration of proteins through mucosa is a method already used and that the various areas of mucosa of the most interest include the nasal, vaginal and sublingual.

The surface area of the nasal cavity of the human adult is approximately 180 cm^2 (Schreider J.P. "Comparative anatomy and function of the nasal passages" in "Toxicology of the nasal passages" C.S. Barrow ed., Hemisphere Publ. Corp., Washington D.C., pp 1-23, 1986). After passing through the vestibular area, the epithelial covering is largely of the pseudostratified respiratory type consisting of basal, intermediate, muciparous and columnar cells. The basal cells are regenerative cells; the intermediate cells are as yet not clearly differentiated columnar or muciparous cells. The muciparous cells secrete mucus which forms a protective supra-epithelial layer and constitutes a first barrier to the passage of substances through the mucosa. The columnar cells are in the majority, have apical microvilli and may be ciliated or non-ciliated. The ciliated cells beat the cilia at a frequency of approximately 15 beats/sec, pushing the mucus towards the throat, thus removing dust particles, bacteria, pollen and allergens trapped in the mucus (mucociliary clearance).

Due to this clearance and drainage, dwell time of the various substances/particles in the nose is fairly short, approximately 3-20 minutes in the human (Duchateau G.S.M.J.E. et al., "Laryngoscope" 95, 854, 1985). The epithelium lies above a highly developed vascular network which has a blood supply of 40 ml/min. in 100 g of tissue (Benda M. et al., "Acta Otolaryngol", 96, 277, 1983).

On this basis, the advantages of administration of drugs by the intranasal route are that:

- unlike parenteral administration, the intranasal administration is not invasive, is generally well tolerated and is easy to self-manage;
- unlike what happens after oral administration, the substance administered does not have to pass through the digestive system of the gastrointestinal tract or undergo hepatic metabolization;
- the available area of nasal mucosa for absorption is relatively large and easily accessible; and
- given that dwell time of the substance in the nose is short, the haematic concentration peak is quickly reached and this can be time by time controlled.

It has therefore been known for some time that drugs and proteins administered through the nasal mucosa act not only locally but at systemic level.

More particularly, the data in the literature concerning proteins and peptides administered by the intranasal route in various animal species, including the human, indicate that bioavailability is over 40% for peptides consisting of 3-6 amino acids (AA), fluctuates around 10-15% for polypeptides consisting of 9-27 AA, drops to less than 1% for polypeptides having higher molecular weight (for example, for insulin - 51 AA - bioavailability is practically zero), although extremely high differences are found, for the same peptides, from species to species, or even from individual to individual of the same species.

This explains why at the end of the 80s only 3 peptides, as such, were being administered by the intranasal route (desmopressin, lypressin, oxytocin), since the early 80s protease inhibitors and enhancers of passage through the nasal mucus had been studied. These enhancers are capable of increasing solubilisation of substances or fluidifying mucus, but they are essentially surfactants which, by more or less

profoundly and reversibly damaging mucosa, increase its passive permeability. Due to this action it has been possible to achieve formulations for intranasal administration of calcitonin (32 AA), insulin (51 AA), growth hormone (191 AA) and other proteins or polypeptides with high molecular weight [Lee W.A., Longenecker J.P. "Biopharm. Manufact.", pp. 1-7, April 1988; Verhoef J.C. et al., "Eur. J. of Drug Metab. and Pharmacokin." 15, 83 (1990); Mishima M. et al. "J. Pharmacobio-Dyn." 10, S-69 (1987); Mishima M. et al. "J. Pharmacobio-Dyn." 12, 31 (1989); Watanabe Y. et al. "Chem. Pharm. Bull." 40, 3100 (1992); Schipper N.G.M. et al. "Pharmaceutical Res." 10, 682 (1993); Shao Z. et al. "Pharmaceutical Res." 11, 1174 (1994)]. Nevertheless, because all these enhancers cause more or less marked toxic effects in the mucous membrane and cilia, their use is not recommended for long-term treatment.

It is furthermore known that dwell time on the mucous membrane of substances administered by the intranasal route is relatively short [Benda M. et al., "Acta Otolaryngol." 96, 277, (1983)]. For this reason, various substances capable of prolonging dwell time of proteins on nasal mucosa in order to favour their absorption have been investigated. For example, satisfactory results have been obtained with viscous agents and adhesive polymers (cellulose derivatives, polyacrylic gel, hyaluronic acid esters, starch spheres and the like).

Nevertheless, except for those spheres of starch which are not absorbed because of their size and which due to hydration in the nasal lumen, slowly release the peptides which had been previously incorporated in the preparation (Illum L. et al. "Int. J. Pharm.", 39, 189, 1987, Bjork E., Edman P. "Int. J. Pharm.", 47, 233, 1988), the other agents also cause toxic phenomena which discourage their long-term use.

Vaginal mucosa has been extensively used for administration of steroid hormones. In particular, the use of ring-shaped pessaries made of polymer materials which release a continuous effective dose of hormones without inducing large changes of plasma levels, as is the case with intermittent use of oral contraceptive pills, has proved useful. Once a substance administered by the vaginal route has been absorbed through the mucosa, it is drained off by the venae pudendae and then by the vena cava, preventing its initial passage through the portal circulation and hence initial metabolization at hepatic level.

Up to the present this administration route has been used for administration of topically active drugs (antimycotics, antibacterial and anti-inflammatory agents) and only rarely for administration of proteins. In this respect, the possibility of using this route for administration of calcitonin incorporated in polymeric micro-spheres is already known (Benucci E. et al., "Calcif. Tissue Int.", 56(4), 274, 1995).

Sublingual administration, similarly to administration via the intranasal and vaginal route, enables passage through the liver and consequently enables destruction of the substance administered to be avoided; in addition, absorption of certain substances by this route is very rapid and has proved to be suitable above all for drugs used in the treatment of cardiovascular diseases (Kinlay S. et al. "Am. J. Cardiol.", 78(5), 555, 1996; Bomber J.W. et al. "Am. Fam. Physician.", 52(8), 2331, 1995). Various attempts have been made to administer proteins alone or in association with enhancers by this route, with conflicting results. In fact, negative data have been published for insulin, including when associated with an enhancer (Pillion D.J. et al. "J. Pharm. Sci.", 84(11), 1276, 1995), very variable data for oxytocin (De Groot A.N. et al., "J. Pharm. Pharmacol.", 47(7), 571, 1995) and potentially interesting data for EGF (epidermal growth factor) (Purushotham K.R. et al., "Am. J. Physiol.", 269 (6 Pt 1), G 867, 1995).

There is therefore still a considerable need for a method which increases absorption of proteins through mucosa, especially through nasal, vaginal and sublingual mucous membrane, without causing toxic effects, thus enabling their use in long-term treatments.

It has now surprisingly been found that such a result is obtained by associating a protein with at least one antibody.

A first object of the present invention therefore is a composition for therapeutic or diagnostic use which is capable of administration by the intranasal, vaginal and sublingual route, characterised in that it comprises a protein-antibody complex and at least one pharmaceutically acceptable ingredient.

Preferably, the protein is selected from the group comprising growth factor hormones, cytokines, coagulation factors, neuropeptides, antimicrobial agents, soluble receptors, antigens and antibodies. Of course, if the protein used is an antibody, the antibody will be a suitable anti-antibody.

Typical examples of hormones which control metabolic function and growth are ACTH (adrenocorticotropic hormone); amyline and the peptides associated with diabetes; enterostatin (capable of reducing fat absorption); glucagon and related peptides, peptides similar to glucagon, for example GLP-1 which controls glucose levels in type II diabetes and inhibits appetite in fasted rats; CCK (cholecystokynin) and related peptides, insulin, peptides similar to insulin; pancreastatin, which inhibits insulin secretion and causes increased glucose levels during intragastric administration of glucose; somatomedin C; calcitonins and their precursors, calcitonin gene-related peptides (CGRPs); parathyroid hormone and related proteins; thyroglobulin; gastrin and related peptides; proteinkinase- related peptides.

Typical examples of hormones and growth factors are: insulin-like growth factors; the growth hormone (6-13) which potentiates the action of

insulin; epithelial cell growth factors (EGF), nerve cell growth factors (NGF), hepatocyte growth factors (LGF), megakaryocyte growth factors (MGDF), blood platelet growth factors (PDGF), fibroblast growth factors (FGF), factors which stimulate granulocytes (GSF), transformation growth factors (TGF), erythrotropoietin, stem cell stimulating factors; glial cell-derived neurotrophic factors (GDNF) and brain cell-derived neurotrophic factors (BDNF).

Typical examples of cytokines are: the interleukins (ILs), tumoral necrosis factors (TNFs), the interferons (IFNs) and interleukin receptors.

Typical examples of hormones which control the release or the activity of other hormones are: aldosterone secretion inhibiting factors (ASIF); corticotropic hormone release controlling factors (CRF) and related peptides; gonadotropic hormones release controlling factors (Gn-RH) and related peptides (GAP); prolactin release controlling factors (PIF and PIH); oxytocin; growth hormone release controlling hormone (GH-RH); thyroid hormone release controlling hormone (TSH-RH); melanophore-stimulating hormone inhibiting factor (MSH-IF).

Typical factors controlling coagulation are: fibrin-related peptides and fibronectin fragments; peptides possessing an antithrombotic action (lysyl-α-ketocarbonyl derivatives).

Typical examples of hormones with an antiinflammatory action are the antiinflammatory peptides (PEPTIDES 1, 2, 3); the peptides which control degranulation of mastocytes (MCD PEPTIDES); the tetrapeptide Rigin (which stimulates phagocytosis); anti-IgE antibodies.

Typical examples of hormones which act at cardiovascular level are: the antiarrhythmic peptides; the natriuretic peptides (ANP, BNP, CNP); endothelin and related peptides; sauvagin; corazonin; angiostatin; angiotensin and related peptides; vasopressin and related peptides; urotensin.

Typical examples of neuropeptides are: neurokynins; neuromedins and tachykynins, substance P and related peptides; neuritensin and related peptides; neuropeptide Y; endorphins, dermorphins and peptides related to the precursor of dinorphin/endorphin; encephalin and related peptides; kyotorphins; vasoactive intestinal peptide (VIP) and related peptides; myelin-related proteins; pituitary adeilate cyclase activation peptide (PACAP).

Typical examples of proteins with an antimicrobial activity are: caecoprin; dermaseptin (a powerful antifungal agent); magainin.

The antibody in turn is an immunoglobulin selected from the group comprising the IgM, IgA and IgG categories and fragments thereof. The immunoglobulin may be specific or aspecific. Preferably, it is specific for the complexed protein. Even more preferably, the immunoglobulin is of human origin, obtained by extraction and purification or by biological techniques such as, for example, the recombining DNA method. In turn, the immunoglobulin fragments are, preferably, of the Fc or Fab type.

Generally, the protein-immunoglobulin or protein-fragment complex comprises from 1 to 15,000 protein moles for each immunoglobulin mole or for each immunoglobulin fragment. Preferably, it comprises from 1 to 5,000, and even more preferably from 1 to 500 protein moles for each immunoglobulin mole or immunoglobulin fragment mole.

Typical examples of pathological states which may benefit from treatment with a pharmaceutical composition according to the present invention are the same as those for which, normally, the above-mentioned proteins are administered by a different route.

The pharmaceutical compositions according to the present invention are preferably prepared in suitable dosage forms for intranasal, sublingual or vaginal administration and comprise an effective dose of at least a protein-antibody complex and at least one pharmaceutically acceptable inert ingredient.

Examples of suitable dosage forms are powders and solutions in suitable metering devices for spray or nebulised administration by the intranasal route, and liposome-based formulations, creams, gels, pessaries and suppositories for the vaginal route, and tablets for the sublingual route.

These dosage forms may also contain other conventional ingredients, for example: preservatives, stabilisers, buffers, salts for regulation of osmotic pressure, emulsifiers, aromas, etc.

If required by particular treatments, the pharmaceutical composition according to the present invention may contain other pharmacologically active ingredients whose concomitant administration is useful.

The quantity of protein-antibody complex in the pharmaceutical composition according to the present invention may vary within a wide range dependent on known factors such as, for example, the type of disease to be treated, the severity of the disease, the patient's body weight, the number of daily administrations and the effectiveness of the preselected complex. Nevertheless, the optimum quantity may be easy and routinely determined by a person skilled in the art, in relation to the posology usually used for each specific protein in already known pharmaceutical compositions.

The dosage forms of the pharmaceutical composition according to the present invention may be prepared according to well known methods of pharmaceutical chemistry which include mixing, granulation, dissolution, sterilisation and the like.

The following examples are intended to illustrate the present invention, without limiting it in any way.

EXAMPLE 1

Intranasal Insulin

Male New Zealand White rabbits, weighing approximately 2.5 kg (Charles River) were used; the animals were housed in individual cages, with free access to food and water.

The animals were fasted for 18 hours prior to the experiment and basal glycaemia was checked immediately prior to administration of the preparations under evaluation.

For intranasal administration of the solutions, a 5 ml syringe was used containing 4 ml of air and, instead of the needle, a Gilson tip was fitted (200 µl tipac).

Quantities of 200 µl of solution per nostril were used for the administration; these were rapidly insufflated together with the air contained in a syringe (named "nasinga").

The study solutions contained insulin either alone or associated with various types of immunoglobulins.

The immunoglobulin concentration was chosen in order to give a molar ratio of insulin/immunoglobulin of 4000 : 1.

The experiment was then repeated using the same method until a total of 9-17 rabbits per treatment was reached.

The pharmacodynamic action of the insulin was assessed by determination of glycaemia at 30', 90' and 180' after administration.

Statistical assessment was carried out by univariance analysis (single measurement variance analysis) and multivariance analysis (analysis by repeated measurements) (MANOVA).

Table 1 shows that:

a) the groups were homogeneous with regard to basal glycaemia values;

b) administration of insulin alone (4 mg/rabbit) causes a slight lowering of glycaemia [-5% ($p < 0.05$) in respect of basal glycaemia] as early as 30' after administration.

c) administration of insulin + IgG complex causes a significant reduction of basal glycaemia ($p < 0.05$) 30', 90' and 180' after administration

(-18%, -17% and -12% respectively).

d) administration of insulin + aspecific IgAs complex causes a significant reduction of basal glycaemia (-12%; $p < 0.05$) 30' after administration.

e) administration of insulin + anti-insulin IgG complex is significantly more active ($p < 0.001$) than insulin alone 30' after administration and the action is also maintained after 90' and 180'.

f) administration of insulin + aspecific IgAs complex is significantly more active ($p < 0.001$) in comparison with insulin alone 30' after administration.

TABLE 1

Treatment	Animals (No.)		Glucose mg/ml				glucose in comparison to t_0 (%)		
		time (min.)	0	30'	90'	180'	30'	90'	180'
Insulin	17	mean SD±	1.05 0.07	1.00 0.1	0.99 0.14	1.04 0.13	95.35 6.59	93.88 13.23	98.44 11.74
Insulin + IgGs	17	mean SD±	1.06 0.11	0.88* 0.14	0.88 0.15	0.94 0.16	83 8.85	82.6 10.65	88.17 13.05
Insulin + IgAa	9	mean SD±	1.05 0.1	0.91* 0.09	0.97 0.11	1.02 0.1	87.94 12.2	93.65 16	97.49 10.16

* $p < 0.001$ vs insulin

SD = standard deviation

EXAMPLE 2

Intravaginal insulin

Female New Zealand White rabbits weighing approximately 2.5 kg (Charles River) were used; the animals were housed in individual cages, with free access to food and water.

The animals were fasted for 18 hours prior to the experiment and basal glycaemia was tested immediately prior to administration of the preparations under evaluation.

For intravaginal administration of the solutions, a 1 ml syringe was used, containing 200 µl of a solution of insulin, either alone or in

association with anti-insulin IgG and 500 µl of air. For administration, instead of the needle a probe with rounded end was used, of the type used for intragastric administrations.

For intravaginal administration also the concentration of immunoglobulin was chosen to give a molar ratio insulin/immunoglobulin ratio of 4000 : 1.

The experiment was carried out on 2 different days, by the same methods, until a total of 4 rabbits per treatment was attained.

The pharmacodynamic action of insulin was assessed by determination of glycaemia at time 0, 30' and 60' after administration.

Table 2 shows that:

a) variance analysis of the differences in comparison with the basal values shows an effect at 30' after administration ($p = 0.0132$) in both groups;

b) intergroup analysis shows a significantly higher action ($p = 0.0281$) (reduction of glycaemia of -22% in comparison with the basal value) in the group treated with the insulin + anti-insulin IgG complex in comparison with the group treated with insulin alone (reduction of glycaemia of -9% in comparison with the basal value).

TABLE 2

			Glucose mg/ml			glucose in comparison with t_0 (%)	
			time (min.)			time (min.)	
Treatment	Animals (No.)		0	30	60	30	60
Insulin	4	mean SD±	1.1 0.08	1.0 0.05	1.0 0.04	91.36 8.50	98.43 7.43
Insulin + IgGs	4	mean SD±	1.1 0.06	0.8 0.22	1.0 0.14	77.23 17.17	97.38 8.17

SD = standard deviation

Working in the same way as described in the previous Examples 1 and 2, positive results can also be obtained with the following proteins: glucagon, calcitonin, ANF, oxytocin, IL-2, IL-8, parathyroid hormones 1-34 and 1-38, tetanic toxin, PACAP.

CLAIMS

1. A composition for therapeutic or diagnostic use, suitable for administration by the intranasal, vaginal and sublingual route, characterised in that it comprises a protein-antibody complex and at least one pharmaceutically acceptable ingredient.
2. A composition according to claim 1, characterised in that the protein is selected from the group comprising hormones, growth factors, cytokines, coagulation factors, neuropeptides, antimicrobial agents, soluble receptors, antigens and antibodies.
3. A composition according to claim 1 or 2, characterised in that the antibody is an immunoglobulin selected from the group comprising IgM, IgA, IgG and fragments thereof.
4. A composition according to claim 3, characterised in that the immunoglobulin is aspecific for the complexed protein.
5. A composition according to claim 3 or 4, characterised in that the immunoglobulin is of human origin.
6. A composition according to any of the claims from 1 to 5, characterised in that the protein-immunoglobulin complex comprises from 1 to 15,000 moles of protein for each mole of immunoglobulin.
7. A composition according to any of the claims from 1 to 5, characterised in that the protein-immunoglobulin complex comprises from 1 to 5,000 moles of protein for each mole of immunoglobulin.
8. A composition according to any of the claims from 1 to 5, characterised in that the protein-immunoglobulin complex comprises from 1 to 500 moles of protein for each mole of immunoglobulin.

INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/EP 98/00650

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 91 07418 A (XOMA CORP ;GREEN CROSS CORP (JP)) 30 May 1991 see page 9, line 22 - page 10, paragraph 1 see page 11, paragraph 4 - page 12, paragraph 1 ---	1,2,4-8
X	EP 0 305 967 A (CIBA GEIGY AG) 8 March 1989 see page 3, line 14 - line 44; claims ---	1-8
X	WO 96 22024 A (BRIGHAM & WOMENS HOSPITAL ;UNIV BRANDEIS (US)) 25 July 1996 see page 7, line 32 - page 10, line 29 see page 12, line 15 - line 18 see page 13, line 3 - line 14 see page 14, line 9 - line 10 --- -/--	1-8

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 May 1998	27.05.98

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 95 13831 A (SCHEPENS EYE RES INST) 26 May 1995 see page 4, line 30 - line 33 see page 5, line 21 - line 34; claims 1,4,8,9	1-8 1-8
X	WO 94 14475 A (TANOX BIOSYSTEMS INC) 7 July 1994 see claims	1-8
E	WO 97 32572 A (PENN STATE RES FOUND ;MASSACHUSETTS INST TECHNOLOGY (US)) 12 September 1997 see page 14, line 10 - page 15, line 12; claims 1,8-12,15	1-8
E	WO 97 15296 A (THERATECH INC) 1 May 1997 see page 22, line 18 - line 36	1-8
X	OIEN, NANCEE L. ET AL: "Induction of local and systemic immunity against human respiratory syncytial virus using a chimeric FG glycoprotein and cholera toxin B subunit" VACCINE (1994), 12(8), 731-5 CODEN: VACCDE;ISSN: 0264-410X, 1994, XP002050972 see page 732, column 1, paragraph 3 see abstract	1-8
Y	WO 90 02135 A (OFFORD ROBIN EWART) 8 March 1990 see page 6, line 12 - line 23 see page 10, line 18 - page 11, line 8	1-8

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INTERNATIONAL SEARCH REPORT

In ational application No.
PCT/EP 98/00650

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-8
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

In view of the large number of compounds which are designed by the compounds mentioned in the claims. the search had to be restricted for economic reasons. The search was limited to the compounds for which pharmacological data was given and / or the compounds mentioned in the claims or examples. and the general idea underlying the invention.

3. ☐ (see guidelines. Part B. Chapter III. Paragraph 3.6)
Claims searched incompletely: 1- 8
Claims searcned completely:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

...ormation on patent family members

Interna...al Application No
PCT/EP 98/00650

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